

**Europäisches
Patentamt****European
Patent Office****Office européen
des brevets****Bescheinigung****Certificate****Attestation**

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03029359.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



Europäisches
Patentamt

PCT/EP200 4 / 0 5 3 6 0 8
European
Patent Office

Office européen
des brevets

Anmeldung Nr:
Application no.: 03029359.1
Demande no:

Anmeldetag:
Date of filing: 19.12.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Octapharma AG
Seidenstrasse 2
8853 Lachen
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

A universally applicable virus inactivated blood plasma produced from portions of
non-caucasian plasma

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K35/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

5

A universally applicable virus inactivated blood plasma
produced from portions of non-Caucasian plasma

10 The present invention relates to a blood plasma pooled from donors which are substantially of non-Caucasians, a pharmaceutical preparation comprising the blood plasma of the invention and the use of the blood plasma of the invention for the manufacturing of a medicament.

Background of the invention

15 Blood groups and the inherent inter-individual differences in human blood were discovered by Karl Landsteiner. The ABO blood group system comprises 4 main phenotypes; O, A, B, and AB, the phenotype being governed by codominant alleles at the ABO locus on chromosome 9.

20 Transfusion of ABO-identical or compatible plasma, such as FFP of specific blood groups is an effective and generally well tolerated treatment of various types of complex or isolated coagulation factor deficiencies, in thrombotic thrombocytopenic purpura, and in repeated large volume plasma exchange. However plasma transfusion in principle carries some risk of adverse events among recipients, which include both transmission of infectious and non-
25 infectious diseases.

Non-infectious adverse events typically occur when immunologic incompatibility between e.g. transfused donor red blood cells and recipient antibodies produce accelerated destruction of transfused cells. According to Landsteiner's law, any human individual has antibodies in plasma if the
30 corresponding antigen is absent from the red blood cells. For example, by infusing plasma from a group A donor to a group B patient, anti-B antibodies from donors plasma will react with and lead to destruction of the patient's red blood cells. Similarly, plasma from a group B donor, which contains anti-A

- 2 -

5 antibodies, is incompatible with a blood group A patient; and plasma from a group 0 donor, which contains both anti-A and anti-B antibodies, is incompatible with a patient having blood group A, B, or AB. Therefore, the blood types must be matched to avoid a reaction based on ABO incompatibility.

10 In addition to non-infectious adverse events, many infectious agents, including viruses, bacteria, and parasites, can be transmitted through blood transfusion. Well recognized viruses include hepatitis A virus (HAV), hepatitis B Virus (HBV), hepatitis C Virus (HCV), human immunodeficiency virus types 1 and 2 (HIV-1/2), and human parvovirus (PV). The risk of transmission of viral
15 Infections is minimized by the introduction of donor screening and new test procedures, and in particular, by the introduction of virus inactivation and/or virus removal procedures. Such procedures include virus inactivation by solvent detergent treatment (EP-A-0 131 740), irradiation, and pasteurization, or virus removal by nanofiltration.

20 Solvent detergent treated human plasma with specific blood groups, such as Octaplas® of blood groups A, B, 0, or AB (Octapharma AG Switzerland), was already developed as an alternative to FFP in order to prevent virus transmission.

Universally applicable plasma in principle can be obtained by using only AB
25 plasma, which contains neither anti-A nor anti-B antibodies (IgM and IgG), thus is compatible with any patient regardless of his blood group. However, the frequency of AB donors (4%) is limited. A plasma suitable for universal transfusion is obtained, if anti-A and/or anti-B antibodies from blood group B and A donors, respectively are removed and/or neutralised by optimal mixing
30 of plasma with the different blood groups. Such neutralization of antibodies was already described (WO-A-99/07390) by mixing 6 to 10 parts of blood or blood plasma of blood group A, 1 to 3 parts of blood or blood plasma of blood group B, and optionally 0 to 1.5 parts of blood or blood plasma of blood group AB without admixing substantial amounts of blood or blood plasma derived
35 from blood group 0.

- 3 -

5 All human races in principle share the same blood system, although the frequency of the four main ABO blood groups varies in populations throughout the world. Measuring the titres of anti-A and anti-B antibodies, it was surprisingly found that not only the frequency of ABO blood groups but also the titers of blood group specific antibodies differ between different ethnic
10 groups. In the Caucasians, in general, the titers of anti-A in group B and group O subjects tend to be higher than the titers of anti-B in group A and group O subjects. On the contrary, in people with non-Caucasian background, such as African-American, Hispanic or Native-American donors, anti-B is almost as high as anti-A titers. Consequently, mixing Caucasian plasma with a considerable
15 portion of non-Caucasian origin at the above mentioned ratios, no optimal neutralization of blood group specific antibodies was found. For example, by mixing of 7 parts of blood group A plasma with 3 parts of blood group B plasma, a considerable portion of which was collected from non-Caucasian donors, high anti-B titres, both of IgM and IgG-type, were found in the plasma
20 pool mixture.

Description of the invention

One object of the invention was to develop a further applicable virus
inactivated blood plasma, which is produced by optimal mixing of blood plasma
25 of different blood groups, obtained from blood or plasma of Caucasian origin and portions of non-Caucasian donors, such as donors of African-American, Hispanic and native American origin, facilitating an optimal neutralization of blood group specific antibodies in the mixture.

This object is solved by a blood plasma pooled from donors which are
30 substantially of non-Caucasians for human use obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group O which comprises

- 4 -

- 5 - four to eight parts of blood or blood plasma from donors having the blood group A,
- more than three to seven parts of blood or blood plasma from donors having the blood group B,
- 10 - zero to two parts of blood or blood plasma from donors having the blood group AB and
- essentially zero parts of blood or blood plasma from donors having the blood group O.

15 In the blood plasma product of the invention, ABO blood group specific antibodies are essentially neutralized by free blood group substances by an optimal mix of different blood groups, and therefore, this plasma can be transfused regardless of the patient's ABO blood group. Therefore, the blood plasma of the invention further reduces both, the risk of transfusion related infections as well as ABO incompatibility related fatalities.

20 In another embodiment of the invention the blood plasma mixture is composed of

- five to six parts of blood or blood plasma derived from donors with blood group A,
- 25 - four to five parts of blood or blood plasma derived from donors with blood group B,
- zero to one part of blood or blood plasma derived from donors with blood group AB, and
- substantially no blood or blood plasma derived from donors with blood group O.

30 The ABO blood group specific antibody titre of the blood plasma of the invention is in particular lower than 16 for anti-A and anti-B IgM antibodies, and lower than 64 for anti-A and anti-B IgG antibodies. In another mixture of the blood plasma of the invention, the titre of the anti-A and anti-B IgM

- 5 -

5 antibodies is lower than 8, and the titre of anti-A and anti-B IgG antibodies is lower than 32, employing assays known to a skilled person and described in the European Pharmacopeia (Indirect Coombs Test).

Preferably, the blood plasma of the invention is inactivated by the method of EP-A-131740, known as solvent/detergent treatment, irradiation,
10 pasteurisation and/or nanofiltration. A typical solvent/detergent-treatment is for instance use of detergents such as oxyethylated polyphenols, like Triton-X-100, and/or polyoxyethylene derivatives of fatty acids such as Tween 80 and tri-N-butylphosphate (TNBP), or combinations thereof. Also medium to long-chain fatty acids or salts thereof, both saturated and unsaturated, preferably
15 caprylic acid or its salts, can be used for virus inactivation. Other methods are irradiation, pasteurization or nanofiltration. All these methods are known to the person skilled in the art.

Preferably, the blood plasma of the invention is frozen or lyophilized.

The blood plasma of the invention shows coagulation activities comparable to
20 fresh frozen plasma.

The present invention is further illustrated by the following example.

Example 1

190 kg of fresh frozen plasma of blood group A, 156 kg of plasma of blood
25 group B, and 34 kg plasma of blood group AB, all obtained in a considerable portion from non-Caucasian donors, are mixed after thawing at +37 °C. The obtained plasma mixture is virus inactivated by using the solvent detergent method. After removal of the virus inactivating reagents and freeze-drying, the amount of free anti-A and anti-B antibodies of both IgM and IgG-type is
30 measured. The titre of anti-A and anti-B antibodies of IgM-type is lower than 8 and the titer of anti-A and anti-B antibodies of IgG-type is lower than 32.

- 6 -

5 Example 2

205 kg of fresh frozen plasma of blood group A, and 137 kg of plasma of blood group B, all obtained in a considerable portion from non-Caucasian donors, are mixed after thawing at +37 °C . The same procedure as in example 1 was used. The titre of anti-A and anti-B antibodies of IgM-type are lower than 8
10 and of IgG-type lower than 32.

- 7 -

5

Claims

1. A blood plasma pooled from donors which are substantially of non-Caucasians for human use obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group O characterized in that
 - 10 - four to eight parts of blood or blood plasma from donors having the blood group A,
 - more than three parts to seven parts of blood or blood plasma from donors having the blood group B,
 - zero to two parts of blood or blood plasma from donors having the blood
 - 15 group AB and
 - essentially zero parts of blood or blood plasma from donors having the blood group O.
2. The blood plasma according to claim 1 virus-inactivated by any virus inactivation or virus removal method.
- 20 3. The blood plasma according to claim 2 wherein the blood plasma was inactivated by solvent/detergent treatment, irradiation, pasteurisation and/or nanofiltration.
4. The blood plasma according to claim 3 wherein the virus inactivation was performed by using detergents such as oxyethylated polyphenols, like Triton-X-100, and/or polyoxyethylene derivatives of fatty acids such as Tween 80 and tri-N-butylphosphate (TNBP), or combinations thereof.
- 25 5. The blood plasma according to claim 3 virus inactivated by treatment with long-chain fatty acids, such as caprylic acid or the respective salts.
- 30 6. The blood plasma according to any of the forgoing claims substantially free of virus inactivating agents.

- 8 -

- 5 7. The blood plasma of any one of the foregoing claims having ABO blood group specific antibody titre lower than 16 for anti-A and anti-B IgM antibodies, and lower than 64 for anti-A and anti-B IgG antibodies.
8. The blood plasma of any of the foregoing claims in liquid, frozen, dried, or lyophilised form.
- 10 9. A pharmaceutical composition comprising the blood plasma of any one of the claims 1 to 8.
10. Use of the blood plasma of any of the foregoing claims for the manufacturing of a medicament for the treatment of coagulation factor deficiencies, thrombotic purpura, and in repeated large volume plasma
- 15 exchange.
11. A process for manufacturing the blood plasma of any one of the claims 1 to 8 by admixing
- four to eight parts of blood or blood plasma from donors having the blood group A,
 - 20 - more than three parts to seven parts of blood or blood plasma from donors having the blood group B,
 - zero to two parts of blood or blood plasma from donors having the blood .. group AB and
 - essentially zero parts of blood or blood plasma from donors having the
 - 25 blood group O.

- 9 -

5

Abstract

A blood plasma pooled from donors which are substantially of non-Caucasians for human use obtainable by mixing blood or blood plasma of blood groups A and B, optionally AB without admixing substantial amounts of blood or blood plasma of blood group O characterized in that

- 10 - four to eight parts of blood or blood plasma from donors having the blood group A,
- more than three part to seven parts of blood or blood plasma from donors having the blood group B,
- zero to two parts of blood or blood plasma from donors having the blood
- 15 group AB and
- essentially zero parts of blood or blood plasma from donors having the blood group O.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP04/053608

International filing date: 20 December 2004 (20.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 03029359.1
Filing date: 19 December 2003 (19.12.2003)

Date of receipt at the International Bureau: 18 January 2005 (18.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record.

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.